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The need for serum biomarker development for diagnosing and excluding tubal ectopic pregnancy

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Keywords

Tubal ectopic pregnancy; biomarker; cost; diagnosis

Tubal ectopic pregnancies occur in 1–2% of pregnancies in the developed world and remain a leading cause of pregnancy-related first trimester deaths (1,2). In the developing world, the incidence is much higher: one in ten women admitted with a diagnosis of tubal ectopic pregnancy ultimately die from the condition (3). Tubal ectopic pregnancy is also a considerable cause of maternal morbidity. In the short-term, morbidity includes pelvic pain, need for blood transfusion and complications of treatment. In the long-term, morbidity, such as fertility prospects, depends on the clinical features of the ectopic pregnancy (i.e. whether it occurred in a woman using contraception, whether there was Fallopian tube rupture, whether there was evidence of contralateral tubal disease) and the type of treatment chosen (4). Short- and long-term consequences on health-related quality of life and psychological issues (such as bereavement) are important, but are rarely quantified.

Tubal ectopic pregnancy is one of few medical conditions that can be treated expectantly, surgically or medically. Although the exact proportion is not known, it is well known that some tubal ectopic pregnancies resolve spontaneously, often without any significant symptoms. Expectant management is therefore a viable option in selected cases, such as clinically stable, asymptomatic women with falling serum beta-human chorionic gonadotropin (hCG) levels. Laparoscopic salpingectomy (excision of the Fallopian tube) is the current surgical treatment of choice due to the theoretical risk of recurrence in a damaged Fallopian tube (4). Salpingostomy (when a linear incision is made in the Fallopian tube to remove the ectopic pregnancy) is usually performed when the contralateral tube is abnormal. However, results are still awaited from a large randomized trial comparing salpingectomy against salpingostomy (5). Medical treatment relies on using agents to pharmacologically induce tubal abortion or 'dissolve' a growing ectopic pregnancy. A single dose (or multi-dose regimen) of intra-muscular methotrexate, a folic acid antagonist, in the out-patient setting has been used for the treatment of ectopic pregnancy for over 20 years in the developed world and there is now an increasing volume of experience with this therapy (4,6).

Whether expectant, surgical or medical, it is important that treatment is instigated early to reduce morbidity and mortality. However, the diagnosis of tubal ectopic pregnancy

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Andrew Horne and Professor Hilary Critchley have received funding for research into ectopic pregnancy from the Chief Scientist's Office (AH, HC), Wellbeing of Women (AH, HC) and the Medical Research Council (AH). They also hold a patent for a diagnostic biomarker for ectopic pregnancy (# 0712801.0).

(currently a combination of ultrasound and serum hCG measurement) remains problematic often resulting in treatment delays. Fewer than 50% of tubal ectopic pregnancies are diagnosed at the patient's initial presentation (7,8). Despite clinical advances in imaging, ultrasound is non-conclusive in up to 18% of women for whom measurement of serial hCG concentrations is necessary to guide management (8). Further difficulties are encountered because serial hCG determination cannot accurately separate arrested intrauterine from tubal ectopic pregnancies. Decelerated increases in hCG concentrations cannot be used to discriminate between a miscarriage and an ectopic pregnancy. Moreover, laparoscopy can be occasionally required to confirm the diagnosis and this is a procedure that is not without risk to the patient. The inevitable multiple visits and tests currently necessary are a sizeable expense for health services. As an example, we refer to data from a recent study performed in Edinburgh that indicate that health services in Scotland are spending up to £1.5 million per year diagnosing and excluding ectopic pregnancy (an estimated £9 million in direct costs alone to health services per year throughout the United Kingdom alone) (9).

Over 20 serum biomarkers have been identified to date in an attempt to permit earlier diagnosis of ectopic pregnancy, the instigation of earlier management and reduce healthcare costs (10,11). Certain serum biomarkers have been shown initially to be of discriminatory value but then subsequent studies have found them to be of limited use (such as placental protein 14) (12,13). A number of biomarkers (such as estradiol, pregnancy associated plasma protein A, cancer antigen 125) can distinguish a tubal ectopic from a viable intrauterine pregnancy but are unable to distinguish the former from a non-viable intrauterine pregnancy (miscarriage) (13-16). Other markers (such as vascular endothelial growth factor, creatinine kinase and progesterone) have been studied extensively in relation to ectopic pregnancy but the results have been so conflicting that none have been put into clinical use (13,16,17).

The clinical utility of these biomarkers is limited because of variable results due, for the most part, to limitations in study design. In many studies, the cohort examined was very small and the prevalence of ectopic pregnancy within the study population was not constant. In some studies, patients were not accurately matched for gestation. This reflects the difficulty in determining the gestational age of an ectopic pregnancy. Some of the serum biomarkers also limited their own use, as they did not follow a steady pattern (increase or decrease) with a normal gestation. Moreover, changes in the serum assays and the reagents used to detect the biomarkers over the decades have led to conflicting results between studies.

Nonetheless, it is clear from Scottish data that a diagnostic serum biomarker would at the very least be cost effective in Europe and the USA (9). However, to have significant impact on the case mortality and morbidity rate associated with tubal ectopic pregnancy in developing countries, it would need to be one that would be accurately and quickly assayed, preferably in an emergency department setting. Furthermore, such a test would have to be low cost to measure to have true clinical utility. In the post-genomic era, new candidate biomarkers are being identified using genomic technology (18,19). For example, the recent demonstration of inhibin/activin beta-B under-expression in the decidualized endometrium of women with tubal ectopic pregnancies, associated with lower serum activin B concentrations, indicates that further potential biomarkers of tubal ectopic pregnancy could be discovered by focusing on secreted proteins associated with uterine decidualization (18). This approach raises the possibility of using multiple serum biomarker analysis in order to diagnose tubal ectopic pregnancy. However, we believe that progress will only be made in biomarker development when significant resources are invested into testing these candidates in large gestation-matched cohorts, in both prospective and longitudinal studies, and in the relevant health settings.

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